REMARKS

Claims 49-56, 73-75, 79, 83 and 85 were pending in this application. Without conceding to the merits of the rejections, and in order to expedite prosecution of the application, claims 49-56, 73-75, 79, 83 and 85 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims in this application and/or a related application. New claims 86-107 have been added herein. No new matter has been added by way of this amendment, and support can be found in the originally filed specification and claims. The recitations in new claims 86 and 87 essentially parallel those in cancelled claims 49, 50, 55 and 56. Support for new claim 88 can be found, *e.g.*, on page 4, lines 19-24; page 15, line 24 - page 16, line 7; and page 24, lines 5-30. Support for new claims 89 and 90 can be found, *e.g.*, in original claim 4 and cancelled claim 52. Support for new claims 91-93 can be found *e.g.*, at page 41, lines 4-6. The recitations in new claims 94-96 parallel those in cancelled claim 53. The recitations in new claim 97 parallel those in cancelled claim 73, which the Examiner found to be allowable if rewritten in independent form (Office Action, page 8). The recitations in new claims 98 and 99 parallel those in cancelled claim 74. The recitations in new claim 100 parallel those in cancelled claim 75. Support for new claim 101 can be found, *e.g.*, at page 21, lines 3-5. The recitations in new claim 102 parallel those in cancelled claim 83, which the Examiner found to be allowable if rewritten in independent form (Office Action, page 8). The recitations in new claims 103-107 parallel those in cancelled claim 85.

As amended, the claims now recite methods for preventing, and methods of treating, a respiratory syncytial virus-induced disease, comprising administering to a patient a high affinity neutralizing immunoglobulin that specifically binds to a RSV F antigen with a K_a of at least 10^{10} M^{-1} as measured by surface plasmon resonance, wherein the high affinity neutralizing immunoglobulin binds to the same epitope on the RSV F antigen as the antibody composed of a VH having the amino acid sequence SEQ ID NO:2 (Figure 1B) and a VL having the amino acid sequence SEQ ID NO:1 (Figure 1A).

Thus, following entry of this amendment, claims 86-107 will be pending in this application.

I. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Claim 53 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement (Office Action, pages 2-4). The Examiner opines that the antibody IX-493 is required for practice of the claimed methods and suggests depositing the antibody under the terms of the Budapest Treaty (*Id.* at pages 3-4).

Claim 53 has been cancelled herein thus rendering this rejection moot. Applicants respectfully submit that the rejection should not be applied to the new claims for the reasons detailed below.

The amino acid sequences of antibody IX-493 are provided in the specification, *e.g.*, at page 8, line 17 - page 9, line 2; Figure 1 and Table 2. Methods for cloning an antibody using recombinant techniques were well known and readily available to those skilled in the art at the time of the earliest claimed priority date. Thus, given the guidance provided by the specification combined with the knowledge of the skilled artisan, Applicants respectfully submit that the IX-493 antibody utilized in the claimed methods is enabled. Accordingly, this rejection should not be applied to the new claims.

II. The Rejection Under 35 U.S.C. § 102 Should be Withdrawn

Claims 49, 50, 55 and 85 are rejected under 35 U.S.C. § 102(b) and claims 49, 50, 53-55 and 85 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,840,298 ("Brams") (Office Action, page 5).

Claims 49, 50, 53-55 and 85 have been cancelled herein thus rendering these grounds of rejection moot. Applicants respectfully submit that the rejection should not be applied to the new claims for the reasons detailed below.

New independent claims 86 and 87 recite a method for preventing and a method of treating a respiratory syncytial virus-induced disease, respectively, comprising administering an immunoglobulin that, *inter alia,* (a) is a neutralizing immunoglobulin, (b) binds to an F antigen of RSV with an affinity constant (K_a) of at least 10^{10} M^{-1}, and (c) binds to the same epitope on a RSV F antigen as the antibody composed of a heavy chain variable region (VH) having the amino acid sequence SEQ ID NO:2 (Figure 1B) and a light chain variable region (VL) having the amino acid sequence SEQ ID NO:1 (Figure 1A) (*i.e.*, antibody IX-493).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Brams does not teach neutralizing immunoglobulins that specifically bind to the same epitope on a RSV F antigen as the antibody IX-493 with a K_a of at least 10^{10} M^{-1}. Brams describes two human monoclonal antibodies against a RSV F antigen (*i.e.*, RF-1 and RF-2), neither of which have the features of the immunoglobulins utilized in the claimed methods.

Applicants direct the Examiner's attention to Heard *et al.* (1999) *Mol. Med.* 5:35-45 ("Heard"), and Chamat *et al.* (1999) *J. of Infect. Dis.* 180:268-277 ("Chamat"), submitted herewith as References C03 and C04, respectively, on the Supplemental Information Disclosure Statement (IDS), as well as the Declaration under 35 C.F.R. § 1.132 by Dr. William Dall'Acqua ("the Dall'Acqua Declaration") also submitted herewith.

Heard is a scientific article published by five of the six co-inventors listed on Brams, which describes data relating to RF-1 and RF-2. In discussing the results of virus neutralization studies, Heard states that "cRF-1 did not effectively inhibit virus infection *in vitro* in the absence of complement (data not shown), indicating that it <u>does not bind a neutralizing epitope</u>" (page 43, left column, lines 8-11; emphasis added). "cRF-1" is a monoclonal RF-1 antibody produced in Chinese Hamster Ovary (CHO) cells. The amino acid sequence encoding cRF-1 is identical to that of the RF-1 antibody disclosed in Brams, *e.g.*, compare the amino acid sequence of RF-1 VH and VL domains presented in Figure 1 (top) and Figure 2 (top) of Heard, respectively, with those

in Figure 8b and 7a of Brams, respectively.[1] Thus, the RF-1 antibody described in Brams is not a neutralizing immunoglobulin, *i.e.*, an immunoglobulin that reduces the replication of RSV as measured in a microneutralization assay lacking complement.

Chamat is a scientific article published by four of the six co-inventors listed on Brams which describes data relating to RF-1 and RF-2. Chamat states that "RF-1 and RF-2 compete for the same binding site; however, differences in specificity may exist" (page 275; emphasis added).

The Dall'Acqua Declaration describes the results of a competitive binding analysis conducted to investigate whether RF-2 and an example of an antibody encompassed by the claimed invention, motavizumab (formerly known as Numax®), bind to identical sites on a RSV F antigen. As discussed in the Dall'Acqua Declaration, the results of the competitive binding analysis seem to indicate that RF-2 and motavizumab do not bind to identical sites on a RSV F antigen (Dall'Acqua Declaration at ¶14).

Thus, since RF-2 and RF-1 bind to the same binding site on a RSV F antigen (Chamat at page 275), and RF-2 and motavizumab do not bind to identical sites on a RSV F antigen (Dall'Acqua Declaration at ¶14), then RF-1 must also bind to a site on a RSV F antigen that is not identical to the binding site of motavizumab.

As evidenced by Wu *et al.* (2005) *J. Mol. Biol.* 350:126 (submitted herewith as Reference C05 on the Supplemental IDS) and as described in the specification (see, *e.g.*, page 24, lines 5-30), the IX-493 antibody recited in the present claims was used as a template to produce antibodies with better binding parameters for the same epitope of a RSV F antigen as compared to IX-493 in order to generate an antibody with improved properties against RSV. Ultimately, motavizumab was one of the antibodies produced (*see, e.g.*, Wu *et al.* (2007) *J. Mol. Biol.* 368:652, submitted herewith as Reference C06 on the Supplemental IDS).

---

[1] Please refer to the Dall'Acqua Declaration at ¶4 for a discussion of the inconsistencies in the VH and VL chain and domain sequences of Brams.

Accordingly, because motavizumab binds to an epitope of a RSV F antigen that is not identical to the epitope of a RSV F antigen for RF-1 and RF-2 (see discussion above), then IX-493 must also bind to an epitope of a RSV F antigen that is not identical to the epitope of a RSV F antigen for RF-1 and RF-2. Therefore, the RF-1 and RF-2 antibodies described in Brams do not meet every element of the claimed methods either expressly or inherently and, as such, cannot anticipate the claimed methods.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. §§ 102(b) and 102(e) not be applied to the new claims.

III. The Rejection Under 35 U.S.C. § 103 Should be Withdrawn

Claims 49-52, 56, 74 and 75 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Brams and Johnson *et al.* (1999) *J. Infect. Dis.* 180:35-40 ("Johnson") in view of Shreder (2000) *Methods* 20:372 ("Shreder").

Claims 49-52, 56, 74 and 75 have been cancelled herein thus rendering this rejection moot. Applicants respectfully submit that the rejection should not be applied to the new claims for the reasons detailed below.

None of the cited references, alone or in combination, teach or suggest the claimed methods or provide one skilled in the art with a reasonable expectation of success with respect to the claimed methods.

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of

the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467.

The *KSR* Court rejected a rigid application of the "teaching, suggestion, or motivation" test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739 USPQ2d at 1395. However, the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can only be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art.

Thus, the principles set forth in *Graham*—which are still good law post-*KSR*—require that *both* the suggestion and the expectation of success must be found in the prior art, and not derived from knowledge gained from the applicant's disclosure.

After the *KSR* decision, the Board of Patent Appeals and Interferences has continued to shape the contours of the obviousness inquiry. The Supreme Court in *KSR* stated that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1389. Following *KSR*, the Board stated that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *Ex Parte El-Naggar*, WL 2814131 at *3 (BPAI 2007) (citing *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (quoting *In re Wesslau*,

353 F.2d 238, 241 (C.C.P.A. 1965))). Moreover, the Board has also stated that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Ex Parte Altenbuchner,* WL 1766992 at *6 (BPAI 2007) (quoting *In re Kahn*, 441 F3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

The focus of Brams is an efficient method for generating human antibodies. Brams describes two human monoclonal antibodies specific for a RSV F antigen (*i.e.*, RF-1 and RF-2) as examples of human antibodies generated by this method. There is no teaching or suggestion in Brams as to how to produce neutralizing immunoglobulins that specifically bind to the same epitope on a RSV F antigen as the antibody IX-493 with a K_a of at least 10^{10} M^{-1}, as claimed, *much less* any teaching or suggestion to utilize such immunoglobulins to treat or prevent an RSV-induced disease, as claimed. Further, after reading and following the disclosure of Brams, one skilled in the art would have had no motivation or reasonable expectation of successfully producing such a neutralizing immunoglobulin having the features recited in the currently pending claims. Indeed, as discussed above, the RF-1 and RF-2 antibodies generated using the Brams method have different features than those recited in the claims (*see also*, *e.g.*, Heard at pages 42-43).

Johnson does not cure the deficiencies of Brams. Johnson compares the activities of two anti-RSV antibodies, MEDI-493 (Synagis®) and RSHZ19. Johnson does not teach or suggest improving the activities (*e.g.*, the binding parameters) of either of those antibodies, much less any method for doing so. Moreover, one skilled in the art would not have had a reasonable expectation of successfully producing antibodies with improved activities based upon the disclosure in Johnson. Further, given the success of MEDI-493, one skilled in the art would not have had any motivation to try to improve MEDI-493. For example, as discussed in Johnson, as of 1999, MEDI-493 was known to be a highly effective neutralizing antibody that significantly reduced hospitalizations due to RSV infection in a phase III clinical trial (see, *e.g.*, Johnson, Abstract). Further, as of the earliest claimed priority date of the present application (2001) MEDI-493 (Synagis®) had been administered to more than 300,000 infants worldwide and had

become the standard of care for infants at high risk for RSV, with worldwide sales of MEDI-493 totaling $516 million dollars in that year alone (see, *e.g.*, MedImmune, Inc. Annual Report 2001 at page 7; submitted herewith as Reference C07 on the Supplemental IDS). Thus, Johnson, either alone or in combination with Brams, does not render the claimed methods obvious.

Shreder does not cure the deficiencies of Brams or Johnson, either alone or any combination thereof. Shreder relates to the use of haptens as probes of the antibody response. There is no teaching or suggestion in Shreder of any antibody that specifically binds to RSV F antigen, *much less* a neutralizing immunoglobulin that specifically binds to the same epitope of a RSV F antigen as the antibody IX-493 with a K_a of at least 10^{10} M^{-1}. The fact that antibodies can have affinities ranging from 10^5 to 10^{12} M^{-1} does not suggest making an antibody that specifically binds to a RSV F antigen with a K_a of at least 10^{10} M^{-1}. Moreover, Shreder does not provide any motivation or reasonable expectation of successfully producing a neutralizing immunoglobulin that specifically binds to the same epitope of a RSV F antigen as the IX-493 antibody with a K_a of at least 10^{10} M^{-1}.

In view of the foregoing, Applicants respectfully submit that the rejection under 35 U.S.C. § 103 should not be applied to the new claims.

IV. Obviousness-Type Double Patenting

Claims 49-55, 74, 75, 79 and 85 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16 of U.S. Patent No. 6,656,467 ("the '467 patent") (Office Action, pages 7-8). Applicants traverse the rejection, and Applicants respectfully request this rejection be held in abeyance until such time as there is allowable subject matter.

V. Conclusion

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for immediate allowance. If the Examiner disagrees, it is requested that the

Examiner call the undersigned at the number listed below to arrange a telephone interview to expedite prosecution of the application.

A three (3) month extension of time is requested and will be paid via EFS-web, which will extend the response period from March 14, 2008 to and including June 14, 2008. Because June 14, 2008 falls on a Saturday, the response period is extended to Monday, June 16, 2008, pursuant to 37 C.F.R. § 1.7. Thus, this response is timely filed. Applicants believe no other fees are due in connection with this Amendment. However, if there are any other fees due, please charge them to Deposit Account 50-3013. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,

Date: June 16, 2008

Tamera M. Weisser, Ph.D. (Reg. No. 47,856)

For: Anthony M. Insogna (Reg. No. 35,203)

JONES DAY
222 East 41st Street
New York, NY 10017-6702
(858) 314-1200